# Chem kin s and l ukocyt traffic

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**Over the past t n y ars, numerou chem kines have been id ntified as attractants of different types of blood leukocytes t sit s f infecti n and inflammation. Th y are produ ed locally in the tissu s and act n l ukocytes through selective receptors. Chemokines are now known to also function as regulatory molecules in leukocyte maturation, traffic and homing of lymphocytes, and the development of lymphoid tissues.**

Last century's pathologists knew that leukocytes emigrate from the blood across the wall of microvessels and accumulate in inflamed tissues. The purpose of this migration, a process called diapedesis, remained unknown until Elias Metschnikoff[1] showed that leukocytes engulf and kill bacteria and recognized diapedesis as a fundamental mechanism of host defence. Today, ten years after the discovery of interleukin (IL)-8, chemokines are seen as the stimuli that largely control leukocyte migration. Chemokines have been in the limelight since 1996, when it was discovered that some of their receptors function as binding sites for AIDS viruses. Obviously, sharing receptors with human immunodeficiency virus (HIV) is not the *raison d'être* of chemokines. ~~Their main business is attracting leukocytes.~~

## The basics

Despite its large size, the chemokine family is remarkably homogeneous, and the properties originally ascribed to IL-8 (ref. 3) are still generally valid for the 40 or so human chemokines that have been described so far. Chemokines are small proteins with four conserved cysteines forming two essential disulphide bonds (Cys1–Cys3 and Cys2–Cys4). CXC and CC chemokines are distinguished according to the position of the first two cysteines, which are either adjacent (CC) or separated by one amino acid (CXC). Chemokines have a short amino-terminal domain preceding the first cysteine, a backbone made of β-strands and the connecting loops found between the second and fourth cysteines, and a carboxy-terminal α-helix of 20–30 amino acids. The backbone has a well ordered structure whereas the N- and C-terminal domains are disordered, especially at their extremities[4]. A protein with two instead of four conserved cysteines, lymphotactin[5], and a chemokine-like structure with three amino acids between the first two cysteines ($CX_3C$ motif) at the N-terminal end of a mucin structure[6,7] have also been described.

The effects of chemokines on leukocytes are mediated by heptahelical receptors coupled to GTP-binding proteins. The most impressive effect is the shape change that is observed within seconds after addition of an attractant to a leukocyte suspension, as shown in Fig. 1 for neutrophils. Polymerization and breakdown of actin leads to the formation and retraction of lamellipodia, which function like arms and legs of the migrating cells. Stimulation also induces the upregulation and activation of integrins, which enable the leukocytes to adhere to the endothelial cells of the vessel wall before migrating into the tissues[8]. Several other rapid and transient responses are characteristic of the activation of leukocytes by chemokines, such as the rise in the intracellular free calcium concentration, the production of microbicidal oxygen radicals and bioactive lipids, and the release of the contents of the cytoplasmic storage granules, such as proteases from neutrophils and monocytes, histamine from basophils and cytotoxic proteins from eosinophils[2,9].

Most chemokines are produced under pathological conditions by tissue cells and infiltrating leukocytes[2,10]. Some chemokines seem to fulfil housekeeping functions, however. They may be involved in leukocyte maturation in the bone marrow, the traffic and homing of lymphocytes, and the mechanisms that ensure the renewal of circulating leukocytes.

## Chemokine–receptor interactions and antagonists

Five receptors for CXC chemokines and eight receptors for CC chemokines have been characterized[11]. As shown in Table 1, most receptors recognize more than one chemokine, and several chemokines bind to more than one receptor, indicating that redundancy and versatility are characteristic for the chemokine system (Fig. 2). CXC- and CC-chemokine receptors (CXCRs and CCRs) only recognize chemokines of the corresponding subfamily. Chemokines have two main sites of interaction with their receptors, one in the N-terminal region and the other within an exposed loop of the backbone that extends between the second and the third cysteine[12]. The N-terminal binding site is essential for triggering of the receptor. It is ~~believed that the receptor recognizes the loop region first~~, and ~~that this interaction is necessary for the correct presentation of the triggering domain~~[12]. Analogues that still bind effectively but do not signal and thus act as receptor antagonists were obtained by amino-acid deletion or modification of the N-terminal region of IL-8 and related CXC chemokines[2], N-terminal truncation of MCP-1, MCP-3 and RANTES[2,13], or N-terminal elongation of RANTES[14] and MCP-3 (ref. 15). Potent CXCR4 antagonists were obtained by modification of the first two N-terminal residues of SDF-1 (ref. 16). Antagonists[2,9] and receptor-blocking antibodies[17] inhibit chemokine-induced responses. The search for antagonists has been boosted by the discovery that chemokine receptors, together with the T-cell differentiation antigen CD4, act as recognition sites for HIV-1 (ref. 18). Chemokines and the HIV surface protein gp120 recognize overlapping receptor epitopes and compete for binding. HIV infection is prevented by chemokines[19–21], but also by chemokine-derived antagonists[14,22], and similar effects can be obtained by

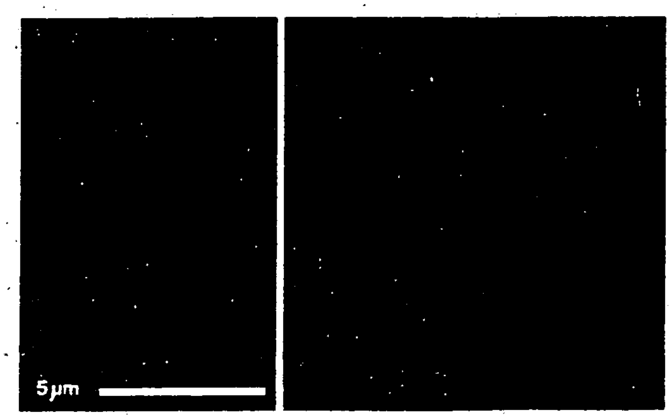


**Figure 1** Shape change of human neutrophil leukocytes. Cells in buffered saline are shown by scanning electron microscopy before (left) and 5 seconds after (right) stimulation with a chemoattractant.

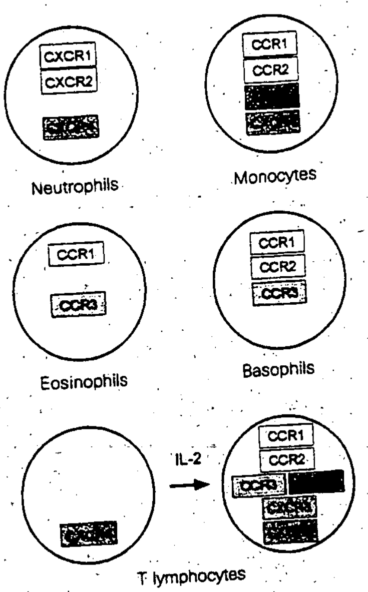


**Figure 2** Main chemokine receptors expressed on human leukocytes. The scheme shows four CXC- and five CC-chemokine receptors that have been extensively characterized in terms of function and binding properties. The SDF-1 receptor, CXCR4, is widely expressed and CCR3 occurs in eosinophils, basophils and (a subset of) T lymphocytes. By far the greatest variety of receptors is seen in T lymphocytes in which expression depends on the state of cell activation. CCR4, CCR6 and CCR7, which are also found in T lymphocytes, are omitted as conditions for their expression are still being investigated.

**Table 1 Human chemokine receptors and their ligands***

| Receptor | Chemokine |
|---|---|
| CXCR1 | IL-8, GCP-2 |
| CXCR2 | IL-8, GROα/β/γ, NAP-2, ENA78, GCP-2 |
| CXCR3 | IP10, Mig |
| CXCR4 | SDF-1 |
| CXCR5 | BCA-1/BLC |
| CCR1 | RANTES, MIP-1α, MCP-2, MCP-3 |
| CCR2 | MCP-1, MCP-2, MCP-3, MCP-4 |
| CCR3 | Eotaxin, eotaxin-2, RANTES, MCP-2, MCP-3, MCP-4 |
| CCR4† | TARC, RANTES, MIP-1α, MCP-1 |
| CCR5 | RANTES, MIP-1α, MIP-1β |
| CCR6 | LARC/MIP-3α/exodus |
| CCR7 | ELC/MIP-3β |
| CCR8 | I-309‡ |
| $CX_3CR1$ | Fraktalkine/Neurotactin |

* The receptors for the lymphocyte-specific chemokines SLC/6Ckine/exodus-2 and DC-CK1/PARK are unknown.
† There is disagreement about the selectivity of CCR4, which was first described as a receptor for RANTES, MIP-1α and MCP-1 and was later shown to be specific for TARC[48].
‡ See references 68, 69.

chemokine-unrelated, low-molecular-weight substances[23]. These findings indicate that the efforts under the AIDS flag may eventually yield antagonists to be used for broader therapeutic applications, for example, in chronic inflammation, autoimmunity, allergic diseases and prevention of transplant rejection.

The rationale for anti-inflammatory therapy based on interference with the chemokine system has been established in animal models[24], as illustrated here by a few examples. Lung reperfusion injury[25] and urate-crystal-induced arthritis[26] in rabbits showed regression after treatment with an anti-IL-8 antibody. Anti-inflammatory effects were also obtained in rat glomerulonephritis with antibodies against MIP-2 (ref. 27), in cutaneous delayed hypersensitivity with antibodies against MCP-1 (ref. 28) and in mouse allergic airway inflammation with antibodies against MIP-1α and RANTES[29]. In view of the redundance among chemokines, neutralization at the receptor level may be more promising, and first encouraging results have been obtained with CC-chemokine antagonists in murine models of arthritis. Administration of an MCP-1 antagonist prevented the onset of arthritis in the MRL-*lpr* mouse and reduced the symptoms once the disease had developed[30], and the antagonist MetRANTES significantly inhibited collagen-induced arthritis in DBA/1 mice[31].

## Allergic inflammation

The observation that RANTES and MCP-3 activate eosinophil and basophil leukocytes, inducing chemotaxis and the release of histamine and leukotrienes, was the first hint that chemokines are involved in allergy[32]. Then eotaxin was discovered, a powerful attractant of eosinophils that immediately gained attention for its potential function in asthma and other forms of allergic inflammation. Eotaxin is expressed in the lungs of animals with asthma and in human tissues where eosinophils accumulate[9]. The eotaxin receptor, CCR3, is present not only in eosinophils but also in basophils[33,34] and a subset of T lymphocytes with $T_H2$ helper properties[35,36]. Whereas basophils and eosinophils release mediators that induce smooth muscle contraction, vascular permeability, mucus secretion, and airway hyperreactivity, T lymphocytes contribute to inflammation by producing cytokines such as IL-4, which enhances IgE production, and IL-5, which primes and activates eosinophils and basophils. It is remarkable that the pathophysiologically relevant leukocytes share CCR3 and can be recruited concomitantly to sites of allergic inflammation by the same chemokines. T lymphocytes expressing CCR3 are found with eosinophils in atopic dermatitis, nasal polyps and ulcerative colitis, whereas the lymphocytes in non-allergic infiltrates are generally CCR3-negative[36]. As shown in Table 1, CCR3 binds several chemokines. Eotaxin and the recently identified eotaxin-2 (ref. 37) bind only to CCR3 whereas RANTES, MCP-2, MCP-3 and MCP-4 also bind to other CC-chemokine receptors[9]. In mice with a deletion of the eotaxin gene, allergen-induced eosinophil infiltration into the lungs is retarded, but the defect is compensated at later stages by other chemokines[38]. A more sustained effect should result from disruption of the gene encoding CCR3.

## T-lymphocyte recruitment

Although lymphocytes were known to accumulate at sites of immune and inflammatory reactions, attractants that induce these responses have been identified only recently. RANTES, MIP-1α and MIP-1β (ref. 2) were the first chemokines for which lymphocyte-chemotactic activity was reported. The monocyte-chemotactic proteins (MCP-1, -2, -3 and -4) are also potent attractants of T lymphocytes, natural killer and dendritic cells[9]. Chemokine-receptor expression varies considerably in lymphocytes. CCR1, CCR2 (ref. 39) and CCR5 (ref. 40) are upregulated by IL-2, whereas other stimulatory conditions, such as exposure to anti-CD3 and/or anti-CD28 antibodies, downregulate receptors and chemotaxis. These observations indicate that T lymphocytes may migrate in response to chemokines after IL-2-mediated proliferation, but not during antigen-dependent activation. Upregulation of chemokine receptors in lymphocytes may enhance susceptibility to HIV infection[40,41]. Unlike many CC chemokines, which attract monocytes, basophils and eosinophils in addition to T lymphocytes, the CXC chemokines IP10 and Mig are selective for IL-2-activated T lymphocytes. They recognize only one receptor, CXCR3, which is restricted to T lymphocytes[42]. Production of IP10 and Mig is induced by interferon-γ (IFN-γ), which inhibits the expression of most other chemokines[2], and this property is a further element of selectivity. In viral infections or delayed-type hypersensitivity reactions, IP10 and Mig are locally upregulated by IFN-γ and available for the recruitment of effector lymphocytes.

Two types of CD4-positive helper T lymphocytes, $T_H1$ and $T_H2$, are distinguished according to the cytokines they produce[43]. As the accumulation of lymphocytes belonging to one or the other subset

influences the course of the local immune response, it was interesting to study the mechanism of recruitment. $T_H1$ and $T_H2$ cells differ in chemokine-receptor expression and their responsiveness to chemokines[35,36,44–46]. CCR5 is expressed preferentially in $T_H1$ cells whereas CCR3 and CCR4 seem to be characteristic of $T_H2$ cells. It can be predicted that chemokine receptors will soon be used as markers for subpopulations of helper T lymphocytes.

### Homeostatic functions in lymphoid tissues

During their development and differentiation, T and B lymphocytes move through different tissue compartments. Although the paths, the rôle of adhesion molecules in the recognition of homing sites, and several highly effective chemokines are known, it is still difficult to understand how this intricate cellular trafficking is regulated[47]. Some pieces of the puzzle, however, are in place. Particularly interesting is a group of newly identified CC chemokines, including TARC, ELC, SLC, LARC and DC-CK1 (see Table 1 for synonyms), which, except for LARC, are expressed constitutively at high levels in the thymus, lymph nodes and other lymphoid tissues. They all attract T lymphocytes and most of them also attract B lymphocytes, which bear selective receptors, namely CCR4 for TARC, CCR6 for LARC, and CCR7 for ELC[48]. DK-CK1 is produced by dendritic cells of germinal centres and T-lymphocyte areas of secondary lymphoid organs and is chemotactic for naive T lymphocytes, suggesting a role in the initiation of an immune response[49]. TECK is produced by thymic dendritic cells and is chemotactic for murine macrophages, dendritic cells and thymocytes[50]. The restricted, constitutive production of these chemokines in lymphoid tissues and their apparent selectivity for receptors expressed by lymphocytes suggest that they are involved in the regulation of physiological lymphocyte traffic.

An example of such a housekeeping function of chemokines comes from observations in mice lacking BLR1, a putative chemokine receptor that is highly expressed in B lymphocytes[51]. Disruption of the BLR1 gene leads to a loss of inguinal lymph nodes and a defective formation of primary follicles and germinal centres in the spleen and Peyer's patches. Receptor-deficient B lymphocytes enter the T-cell areas of these tissues, but fail to migrate into B-cell areas. These results suggested the existence of chemokines that direct lymphocyte homing into specific anatomical areas and regulate the development of functional lymphoid tissues. The ligand for BLR1 (now called CXCR5) is a novel CXC chemokine, BCA-1/BLC, that is expressed in lymphoid tissues and is selective for B lymphocytes[52,53].

A chemokine with potential involvement in lymphocyte maturation and other homeostatic functions is SDF-1, which was originally described as a growth factor for B-lymphocyte precursors[54]. Murine SDF-1 attracts resting T lymphocytes *in vitro* and *in vivo* with unusually high efficacy[55]. Human SDF-1, which differs from its murine homologue by a single residue (Ile instead of Val at position 18) is chemotactic for T lymphocytes, monocytes and neutrophils[20,21], which all express CXCR4 (Fig. 2). The gene encoding CXCR4 was cloned in several laboratories[9] and CXCR4 was later found to act as a co-receptor for T-lymphocyte-tropic HIV-1 strains[18,56]. Mice lacking the SDF-1 gene have severely impaired lymphopoiesis and abnormally low numbers of B-lymphocyte and myeloid bone-marrow precursors[57]. SDF-1 is chemotactic for pro- and pre-B cells, which depend on stromal-cell contact for growth and differentiation, but not for more mature forms[58]. SDF-1 was also shown to induce chemotaxis of CD34-positive cells of different lineages[59]. All these results indicate that SDF-1 may attract progenitor B cells into the microenvironment of stromal cells where growth and differentiation factors are released[58]. More generally, SDF-1 may be involved in directing progenitor cells into the appropriate maturation sites in the bone marrow[59] and may support the colonization of the bone marrow by haematopoietic precursors during embryogenesis[55]. In addition, the finding that mice lacking SDF-1 have a defective ventricular septum of the heart[57] suggests that SDF-1 may not only act on leukocytes and their precursors. A role in morphogenesis is conceivable because SDF-1, unlike most chemokines, is expressed constitutively in several tissues, and its receptor, CXCR4, is found in leukocytes but also in different types of tissue cells[9].

### Future directions

The progress in the chemokine field has been rapid but largely straightforward, and most chemokine actions that have been reported are related to leukocyte migration and recruitment. A major surprise, of course, was the observation that some chemokines block HIV infection[19], which initiated an unprecedented burst of research activity in most leading laboratories in the chemokine and AIDS fields and led to the discovery of chemokine receptors as recognition sites for viral infection[18]. By comparison, other unforeseen developments were less spectacular and have not attracted as much attention and research power. The observation that the Duffy blood group antigen, the recognition site for infection by the malarial parasite *Plasmodium vivax*, binds chemokines was unexpected. DARC (Duffy antigen receptor for chemokines) is a heptahelical receptor that is expressed on erythrocytes, endothelial cells of postcapillary venules and the Purkinje cells of the cerebellum. It binds several chemokines of the CXC and CC subfamilies, but does not signal and its function in this context remains uncertain[60]. Major functions that may not depend on leukocyte migration have been attributed to chemokines, namely the inhibition and stimulation of blood-vessel formation (angiogenesis)[61] and leukocyte maturation in the bone marrow (myelopoiesis)[62,63]. The mechanisms of these effects and the chemokine receptors involved, however, are still being studied.

Where can major advances be expected? One answer that immediately comes to mind is 'lymphocytes'. In view of the identification of several novel chemokine receptors in lymphoid tissues and of lymphocyte-selective chemokines, I am convinced that most migration responses in the complicated trafficking of lymphocytes of different types and degrees of activation will eventually turn out to be mediated by chemokines. Research in this field will open therapeutic opportunities for autoimmune diseases, transplantation and immune deficiencies. Another interesting, therapeutically oriented area is that of chemokine antagonists. Finding antagonists is at present a major goal of many biotechnology and pharmaceutical companies. The prospects are exciting because it has been shown that antagonists are effective, and some low-molecular-weight compounds that block chemokine receptors are already at hand[23]. In addition, new insights into the regulation of leukocyte traffic may be gained by the search for novel chemokines and chemokine receptors with restricted tissue expression. Deletion of chemokine or chemokine-receptor genes, which was very informative in the case of MIP-1$\alpha$ (ref. 62), SDF-1 (ref. 57) and BLR1 (ref. 51), is also a promising approach.

Chemokine activities can also be modulated by interfering with signal transduction, another major area for future research. Most studies so far have used neutrophils or cells transfected with receptors for IL-8, C5a or fMet-Leu-Phe, which signal in similar ways[2,9]. Upon IL-8 binding, receptor coupling with a *Bordetella pertussis* toxin-sensitive G protein, usually of $G\alpha_{i2}$ type, initiates the signalling cascade leading to activation of a phosphatidylinositol-specific phospholipase C, protein kinase C, small GTPases, Src-related tyrosine kinases, phosphatidylinositol-3-OH kinases and protein kinase B[2,9,64]. Phospholipase C delivers two second messengers, inositol-1,4,5-trisphosphate, which releases $Ca^{2+}$ from intracellular stores leading to a transient rise of the cytosolic $Ca^{2+}$ concentration, and diacylglycerol, which activates protein kinase C. Mobilization of $Ca^{2+}$ is essential for granule release and superoxide production, but is not required for the cytoskeletal rearrangements leading to shape change[2]. Phosphatidylinositol-3-OH kinases

can be activated by the βγ subunit of G proteins, small GTPases or Src-related tyrosine kinases[9]. Small GTPases regulate cytoskeletal rearrangements involved in adhesion and chemotaxis[65,66], mediate activation of phospholipase D and are involved in the assembly of the superoxide-forming oxidase[66]. Signalling by other chemokine receptors has not been studied in comparable depth, and virtually no information is available about receptors that mediate homeostatic rather than inflammatory functions of chemokines, for which different signal-transduction mechanisms can be assumed.

A more speculative issue is the possible role of chemokines in bringing or keeping together cells that form a functional unit. This type of attraction has analogy with chemotaxis and has been suggested for the interaction between stromal cells and progenitor B cells[58], and between dendritic cells and naive T lymphocytes[49]. Progress here may be made by concentrating on chemokines that are constitutively expressed in various tissues, such as SDF-1 and HCC-1 (ref. 9), and on chemokine receptors expressed in tissue cells, for example, CXCR4 and receptors found in nerve tissues[67]. *In situ* attraction is only a step away from morphogenesis where cells that form a tissue may initially be kept in close contact by attractants. As mentioned, a potential (direct or indirect) role of chemokines in morphogenesis is suggested by the observation that deletion of the SDF-1 gene led to a defective heart formation[57]. □

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